Remarks

Claims 1-4, 6, 10 are pending. Claim 12 has been added. The Examiner graciously granted an interview on March 3, 2004. The Examiner entered a after- final amendment submitted on February 9, 2004 in response to a September 9, 2004 Office Action. The Examiner indicated that the §112 rejection of the September Office Action would be withdrawn in light of amendments made in the after-final amendment. The Examiner also indicated that the §§ 102 and 103 rejections would stand as for the reasons set forth in the Office Action. The Examiner suggested, however, that the use of the F_3 spacer mutant in the method of claim 1 generated unexpected recombination frequencies and that a claim directed to the F_3 spacer mutant and a specific recombination frequency would be patentable. New claim 12 has been added to address the Examiner's comments.

In regard to the patentability of the other claims, Applicant's assert that they are in condition for allowance.

A. Claims 1-4 and 6 Are Not Anticipated By *Schlake*

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Uion Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); M.P.E.P. § 2131. In addition, "[t]he elements must be arranged as required by the claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990); M.P.E.P. § 2131 (emphasis added). *Schlake* does not disclose (either expressly or inherently), teach, or suggest various aspects of Applicants' claims.

Schlake fails to disclose (either expressly or inherently), teach or suggest at least the following limitations of claim 1: (1) "wherein said cells are vertebrate embryonic stem cells (ES) and said parts of cells are nuclei of vertebrate cells, which can be inserted into ES cells"; and (2) "maintaining the conditions for positive selection during cultivation of said cells

obtained in step b) until exchanging said first DNA expression cassette against said incoming second DNA expression cassette."

Schlake does not teach, suggest, or disclose (either expressly or inherently) "wherein said cells are vertebrate embryonic stem cells (ES) and said parts of cells are nuclei of vertebrate cells, which can be inserted into ES cells" as recited in claim 1. It is undisputed that *Schlake* used BHK and CV-1 cells in its disclosure, and NOT embryonic stem cells (ES). Thus *Schlake* never taught the method in embryonic stem cells as required by claim 1.

The Examiner suggests that *Schlake* teaches that one can use the technique of claim 1 in mouse ES cells. First, the relevant passage of *Schlake*, page 12746, left column, 1st paragraph, reads as follows:

> For higher eukaryotes, homologous recombination is an essential event participating in processes like DNA repair and chromatid exchange during mitosis and meiosis. Recombination depends on two highly homologous, extended sequences and several auxiliary proteins, only part of which has been identified. Strand exchange can occur at any point between the regions of homology, although particular sequences may influence efficiency. These processes can be exploited for a targeted integration of transgenes into the genome of certain cell types like embryonic stem cells. On the other hand, cultured cell lines relevant for genetic engineering purposes have lost the potential to perform homologous recombination at the efficiency that would be required to incorporate it into routine procedures (S. Karreman, GBF, unpublished). We chose BHK, which is one of the two most frequently used lines in biotechnology and has a long track record for the safe production of vaccines.

From the full citation of the relevant paragraph, it is clear for a person skilled in the art that *Schlake* did explicitly decide to <u>not use</u> embryonic stem cells due to known drawbacks. They wanted to use an established <u>cell line</u>, namely BHK and CV-1 cell lines because cell lines have lost the potential for performing homologous recombination. As discussed on page 2 of the pending Application, the frequency of homologous recombination differs widely among cell lines and loci. Throughout the entire reference, *Schlake* does not use,

discuss or mention the potential use of embryonic stem cells (see in particular the section "discussion" on pages 12750-12751). At most *Schlake* teaches that one can try homologous recombination in ES cells. The claimed method is not directed to homologous recombination method but a recombinase mediated expression cassette exchange ("RMCE") method. Therefore, *Schlake* does not teach RMCE, the feature of the claimed method, in embryonic stem cells.

Further, *Schlake* does not teach the features mentioned in step (d) of claim 1, namely to maintain the conditions for positive selection during cultivation of the cells obtained in step (b) until exchanging the first DNA expression cassette against the incoming second DNA expression cassette. The relevant passage in *Schlake* on page 12746, right column, 2nd paragraph, states that "the vector is suited for positive (hygromycin) and negative (gancyclovir) selection" and page 12747, right column, 3rd paragraph, where it is stated that "BHK cells containing a single copy of F_5HygTKF (...) were cultured continuously for 4 weeks (...) **before** they were transfected with 1 μg of F_5NeoF and 2 μg of p0G44. G418-resistant clones isolated after two more weeks were characterized using PCR primers...."

From these passages, it is clear for the person skilled in the art that *Schlake* does not teach to maintain positive selection conditions with hygromycin until the integration of the second DNA expression cassette is complete. Applicants submitted an affidavit from Alfred Nordheim, an expert in the field of stem cell research, particularly regarding embryonic stem cells. Professor Nordheim agrees with Applicants, stating on page 3 of his declaration:

> Schlake and Bode used hygromycin B and gangliclovir for selection (page 12747, left column, fourth paragraph), however, selection conditions are not described as set to maintain the positive selection by hygromycin all the time until the exchange of the first DNA expression cassette against the second incoming DNA expression cassette is completed.

For anticipation under 35 U.S.C. § 102, the reference must teach **every aspect of the claimed invention** either explicitly or impliedly. Any feature not directly taught must

be inherently present (see MPEP § 706.02). For at least these reasons, *Schlake* fails to disclose, either expressly or inherently, each and every element of claim 1, and thus Applicants respectfully request reconsideration and allowance of claim 1, together with all claims that depend on Claim 1. Claims 2-4 and 6 depend from Claim 1, which Applicants have shown above to be allowable, and are allowable for at least this reason, in addition to reciting further patentable distinctions over *Schlake*.

2. The Examiner Fails To Make a Prima Facie Case That Claims 1 and 10 Are Unpatentable Under 35 U.S.C. § 103(a) Over *Schlake* in View of *Jung* or *Ludwig*

A *prima facie* case of obviousness requires three basic criteria:

> First, there must be some suggestion of motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure.
>
> MANUAL OF PATENT EXAMINING PROCEDURE (MPEP), 8th Edition, August 2001, revised February 2003, §2143 (citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Furthermore, "[a] prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention." MPEP §2141.02 (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)).

Obviousness cannot be established by combining the teaching of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the

combination. *ASC Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). This suggestion or motivation may be derived from the prior art reference itself, from the knowledge of one of ordinary skill in the art, or from the nature of the problem to be solved. The basis for a prior art combination, however, must come from a source other than the inventor's disclosure. The Court of Appeals for the Federal Circuit has repeatedly emphasized that hindsight analysis is an inappropriate means for piecing together the elements of an invention from unrelated references. For example, in *In re Fritch*, 972 F.2d 1260, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992), the Federal Circuit stated:

> It is impermissible to use the claimed invention as an instruction manual or 'template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious.

And in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985), the court stated:

> It is error to reconstruct the patentee's claimed invention from the prior art by using the patentee's claim as a "blueprint". When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself.

Here, the Examiner has rejected claims 1 and 10 as being unpatentable under 35 U.S.C. § 103(a) over *Schlake* in view of *Jung*. Applying these standards to the present case, it is clear that the references cited in the latest Action do not support a *prima facie* case of obviousness. The Examiner has failed to establish, however, that the combination of *Schlake* and *Jung* teach or suggest all the limitations of the Applicants' claimed invention.

The Examiner states that *Schlake* mentions ES cell lines, but does not teach the claimed method to create cells which are capable of regenerating an animal. However, *Jung* teaches a method using an ES cell to generate a transgenetic animal. Therefore, the Examiner believes that it would have been *prima facie* obvious for a person skilled in the art at the time the invention was made to use the methods of *Schlake* in BHK cells to modify the genome of

an ES cell using FLP recombinase to create a transgenic animal as described by *Jung*. Further, the Office believes that *Ludwig* is equally suitable to be combined with the disclosure of *Schlake*, because *Ludwig* teaches a method to modify the genome of a fertilized one cell egg using FLP recombinase. Therefore, it would have been *prima facie* obvious for a person skilled in the art at the time the invention was made to use the methods of *Schlake* to modify the genome of fertilized egg using FLP recombinase to create a transgenic animal as described by *Ludwig*. The Examiner cannot account for the fact that none of the references teach all the limitations of the claims 1 and 10.

First, as discussed above, none of the references teach or suggest the features mentioned in step (d) of claim 1, namely "maintaining the conditions for positive selection during cultivation of said cells obtained in step b) **until exchanging said first DNA expression cassette against said incoming second DNA expression cassette**." From passages cited above, it is clear for the person skilled in the art that *Schlake* **does not teach** to maintain positive selection conditions with hygromycin **until exchanging** of the first DNA expression cassette against the second incoming DNA expression cassette is complete. Nor does *Jung* or *Ludwig* teach this claim limitation. Thus, even if there were a suggestion in the art to combine these references, the combination would not render the claims obvious because all the limitations are not present.

In addition, *Schlake*, as already discussed above, clearly states not to use embryonic stem cells but rather suggests to use established cell lines like BHK or CV-1 cells due to their known advantages. Therefore, a person skilled in the art would never have started with the document of *Schlake* and combine it with either *Jung* or *Ludwig*.

Moreover, as Professor Nordheim states on page 7 of his declaration:

> Combining the teachings of Schlake and Bode with either Ludwig et al or Jung et al, the person skilled in the art would not teach the claimed invention. The prior art references ... use embryonic stem cells and murine embryos respectively, the technology disclosed is either classical site-specific

> recombination and/or homologous recombination, which all comprise major drawbacks discussed in the invention. **Therefore, a person starting from the disclosure of Schlake and Bode would not gain any further information from Jung et. al. or Ludwig et al. in order to reach the claimed invention. In particular, a person skilled in the art would not be able to solve the problem of integrated vector sequences or low efficiencies in recombination together with the requirement for an incoming selectable marker.**

A person skilled in the art would not have been able to reach the claimed invention by combining the teaching of *Schlake* with either *Jung* or *Ludwig*.

Nor has the Examiner cited any proper suggestion or motivation for the combination of *Schlake* with either *Jung* or *Ludwig*. Thus, the Examiner has used impermissible hindsight to combine the teachings of these references to attempt to piece together the Applicants' invention. The teaching or suggestion to make the claimed combination must be found in the prior art, not in the applicant's disclosure. (See, MPEP §2143; see also, *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) ("Combining prior art references without evidence of . . . suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight.")).

Finally, secondary considerations warrant against a finding of obviousness. *Schlake* observed targeting frequencies for F3 of .24, .51 and 1.5 % in the BHK and CV-1 cell lines they felt were best suited. In contrast, the claimed invention exhibited targeting frequencies of F18, F21 and F22 of 100%, 54& and 100%, respectively (see page 5 of Nordheim declaration.) Thus, the prior art did not exhibit or ever expect to achieve the high targeting frequencies of the present invention. Indeed, much lower frequencies than that obtained in *Schlake* would have been expected in embryonic stem cells.

The cited art, alone or in combination, fails to teach or suggest the Applicants' invention, as set forth in claims 1 and 10. For these reasons, the Examiner has failed to make

a *prima facie* case of obviousness under 35 U.S.C. §103(a) for the rejection of claims 1 and 10, and the rejection should be reversed.

IX. CONCLUSION

The Examiner rejected claims 1-4, 6 and 10 as being unpatentable under 35 U.S.C. §102(b) over *Schlake* and under §103(a) under *Schlake* in view of either *Jung* or *Ludwig*. However, the Examiner has failed to establish a *prima facie* case of either anticipation or obviousness. In particular, the references cited by the Examiner, alone or in combination, fail to teach or suggest all the elements of presently pending claims. In addition, the Examiner has failed to show a proper suggestion or motivation for combining the references. Therefore, the final rejection of these claims should be reversed.

The fee of $860.00 is enclosed to cover the RCE fee and a three-month extension of time. Please charge any additional fee or credit any overpayment in connection with this filing to our Deposit Account No. 02-3978. A duplicate of this notice is enclosed for this purpose.

Respectfully submitted,

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